REMARKS

Claims

Claims 1–11 are pending with claims 12–16 added by this paper.

Claim Amendments

The claims have been amended to correct for minor typographical errors and to use language in accordance with conventional US practice. It is submitted that the claim amendments do not add new matter.

New claims 12–16 are drawn to additional aspects of Applicants' claimed invention and are supported by the entirety of the disclosure contained in Applicants' instant specification, as originally filed.

Rejections under 35 U.S.C. §101

Applicants appreciate the Examiner's careful reading of the claims. The rejection is moot in view of Applicants' amendments of the claims.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1–3, and 11 stand rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite. Applicants respectfully traverse the rejection.

In the rejection, it is argued that "since the claim does not set forth any steps involved in the method/process, it is unclear what method/process is encompassed." The Office Action further alleges that the claim(s) fail to recite positive steps delimiting how the method/process is actually practiced. Applicants courteously disagree with this contention.

A skilled artisan can readily recognize the literal scope of claim 1 encompasses method embodiments wherein cumulus expansion and oocyte maturation is impaired via, for example, antagonizing the EP_2 receptor and/or inhibiting cyclooxygenase COX-2. One skilled in the art could refer to the disclosure contained in instant specification,

wherein various reagents and/or methods for achieving each claimed embodiment, for example, antagonizing the EP_2 receptor and/or inhibiting COX-2, are discussed in detail. One skilled in the art would instantly recognize what is meant by the term "antagonizing" and/or "inhibiting" in relation to the claimed biological target(s) and the subject area pertaining to the application. Moreover, the specification provides a detailed description on how the structure and/or function of the EP_2 receptor and COX-2, including the method of modulating the activity of such, were both well-recognized in the art. The scientific publications of Norel and Nobel, which are cited in the Office Action, together with Applicants' instant disclosure, provide evidence regarding the mature state of the art prior to the filing of the instant application. The pending rejection fails to appreciate a skilled artisan's understanding of the state of the art, for example, in relation to antagonizing the claimed EP_2 receptor and/or COX-2, and methods for assaying for oocyte maturation and cumulus formation based on the modulation of the claimed receptor types.

In view of the above remarks, it is respectfully submitted that the language of the claims is sufficiently definite, and that one of ordinary skill in the art can readily ascertain whether a given embodiment is within or outside the literal scope of the claims. Nothing more is required under the statute. Withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. §103(a)

The rejection of claims 1–11 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Breyer and Hizaki (primary references) in view of Norel and Nobel et al. (secondary references) is respectfully traversed.

The Office Action contends that one of ordinary skill in the art would have been motivated to employ AH6809 (an EP_1/EP_2 antagonist) and/or celecoxib (a COX-2 inhibitor) in a method of controlling fertility or impairing cumulus expansion and oocyte maturation because the primary references teach that EP_2 receptor disruption and COX-2 inhibition can inhibit ovulation.

To establish prima facie case of obviousness, three basic criteria must be fulfilled. First, there must be some suggestion or motivation...to modify the reference or

to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP §2143.

Therefore according to PTO's own published rules, a *prima facie* case for obviousness can only be established by a showing that the cited references, when taken together, teach/suggest all the limitations of the claimed invention, wherein a method of inhibiting cumulus formation and ooycte maturation comprising at least one of (a) antagonizing an EP_2 receptor; (b) inhibiting COX-2; or (c) comprising antagonizing an EP_2 receptor and inhibiting COX-2, is disclosed.

Each of these aspects will be examined in reference to the cited references.

(a) Antagonizing EP_2 receptor

The cited reference of Breyer discloses the structure of eicosanoid receptor isoforms (EP_{1-4}) and their distinct biological roles when activated by their ubiquitous ligand, PGE_2. Breyer further examines the potential physiological roles of the EP_2 receptor by completely disrupting (i.e., knocking out) said receptor in mice. Among the various physiological defects harbored by these EP_2 mutants, the cited reference teaches that $EP_2^{-/-}$ females (homozygous knockouts) yielded fewer oocyte implantation sites compared to wild-type females. See, Breyer's entire disclosure, particularly, the ABSTRACT and the DISCUSSION sections. The cited reference is silent regarding the claimed use of EP_2 antagonists.

The cited reference of Hizaki also discloses the physiological traits of an EP_2 receptor knockout mouse. It is disclosed that a knockout of EP_2 results in abortive cumulus formation and impaired fertility in homozygous $EP_2^{-/-}$ females. The cited reference postulates that impaired fertilization in $EP_2^{-/-}$ mice is presumably the result of incomplete oocyte maturation because cumulus-oocyte interactions are considered important for the production of fertilization-competent eggs and that the disordered expansion may interfere with these interactions. See, the paragraph bridging pages 10505–10506 of the cited reference. Like Breyer, Hizaki is also silent as to the use of a pharmacological intervention (i.e., antagonists) against the particular receptor subtype(s).

The cited references of Breyer and Hizaki make no mention of EP_2 antagonists and whether such can be used, for example, analogously to the knockout technique, to inhibit oocyte formation in mice. The Office Action has failed to establish that the knockout technique is functionally equivalent to the method disclosed herein. Applicants submit that the two methods are not functionally equivalent. It is readily appreciated in the art that the abrupt and disruptive effects of a knockout technique does not precisely simulate the pharmacological action of an antagonist (as described in the instant invention). In short, since the cited references are silent regarding the use of an EP_2 antagonist for achieving the claimed physiological effect, Breyer and Hizaki, either solely or in combination cannot render obvious the claims of the instant invention.

(b) Inhibiting COX-2

Contrary to the Examiner's assertion, the information relating to COX-2 is not intrinsically disclosed in the cited references of Breyer or Hizaki. Both Breyer and Hizaki utilize several external disclosures to draw a parallel between an EP_2 knockout and a COX-2 deficient mouse with regard to cumulus formation. See, lines 11–14 at page 228 and lines 7–12 at page 229 of Breyer et al. Also, see the paragraph bridging cols. 1 and 2 at page 10501 and lines 3–10 in col. 2 at page 10505 of Hizaki et al. Moreover, neither Breyer nor Hizaki provides any teaching or suggestion on the use of COX-2 inhibitors to yield the claimed physiological effects. The disclosure in Breyer and Hizaki is drawn to COX-2 deficient mice. There is no teaching or suggestion that a COX-2 inhibitor may be used analogously to, for example, a COX receptor knockout mouse, to generate the claimed physiological effect.

(c) Antagonizing an EP_2 receptor and inhibiting COX-2

There is no teaching or suggestion in either Breyer or Hizaki to employ a double knockout of EP_2 receptor and COX-2 (i.e., in the same mouse) for the study of the biological activity of these proteins. A skilled artisan would not be inclined to conduct such a study because the outcome is unknown. However, even if one were to do so, such a double knockout of EP_2 receptor and COX-2 would fail to render obvious the claims of the instant invention because such a disclosure would fail to teach/suggest the claimed use of an EP_2 receptor antagonist and a COX-2 inhibitor.

It is respectfully submitted that chemical (i.e., pharmacological) and genetic (i.e., knockout) approaches to study protein function are not functional equivalents of one another, as assumed in the Office Action. For example, a lack-of-function knockout technique leads to a binary outcome (i.e., observation of a trait in presence of a gene product compared to the lack thereof in the absence said gene) while a chemical approach provides dose-dependent functional modulation. Furthermore, Bryer and Hizaki are silent as to the known extraneous effects of gene knockout, for example, a physiological effect being rendered due to an epistatic effect of a gene during development as opposed to a direct effect of the gene. In view of the above-recited limitations, it is courteously submitted that Breyer and Hizaki, either solely or in combination, fail to teach or suggest all the aspects of the claimed invention.

Secondary references

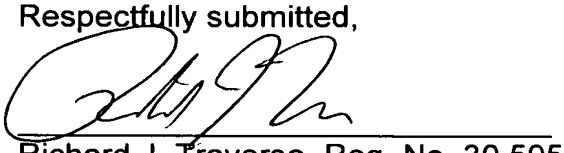
The secondary references are relied on merely to show relevant inhibitors. The additionally cited secondary references of Norel and/or Noble either solely or in combination fail to rectify the deficiencies of the primary references, which are both drawn to the patho-physiological effects of EP receptor and COX-2 gene disruption in an animal (the cited teachings of Bryer and/or Hizaki). For example, the secondary reference of Norel teaches the use of an EP_2 antagonist in the relaxation of bronchial tissues. Noble's disclosure is drawn to the use of COX-2 inhibitors for their anti-platelet activity, anti-arthritic effects, and in the treatment of CHD, diabetes, dehydration or aging. The secondary references offer no guidance or suggestion regarding the use of the claimed agents for inhibiting cumulus formation and oocyte maturation. Moreover, neither Norel nor Noble provides any guidance or suggestion regarding the co-administration of the EP_2 receptor antagonist and a COX inhibitor, especially in relation to attaining the biological effect claimed herein. Therefore, it courteously submitted that the primary references, even in combination with the secondary reference of Norel and Norbert, fail to render obvious what is claimed by the instant invention.

Overall, the cited references, either solely or in combination, fail to disclose a method for inhibiting cumulus formation and oocyte maturation comprising antagonizing an EP_2 receptor and/or inhibiting COX-2. Moreover, since the primary references make no mention of pharmacological intervention comprising administering an antagonist

and/or an inhibitor, the cited references, even at their broadest possible interpretation, fail to render obvious the claimed subject matter. The Office Action has failed to meet the basic criteria for *prima facie* case of obviousness. As such, all the rejections under 35 U.S.C. §103(b) must be withdrawn.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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